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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,550	02/09/2001	Akihiro Funakoshi	053466/0299	5276
22428 7590 03/22/2011 FOLEY AND LARDNER LLP SUITE 500 3000 K STREET NW WASHINGTON, DC 20007				
EXAMINER				
SPECTOR, LORRAINE				
ART UNIT		PAPER NUMBER		
1647				
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary****Application No.**

09/762,550

**Applicant(s)**

FUNAKOSHI ET AL.

**Examiner**

LORRAINE SPECTOR

**Art Unit**

1647

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 06 January 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 14, 16-23, 25, 26, 40 and 41 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.

- 6) ☒ Claim(s) 14, 16-23, 25, 26, 40 and 41 is/are rejected.

- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.

- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 12/21/10, 1/6/11

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Claims 14, 16-23, 25, 26 and newly introduced claims 40 and 41 are pending and under consideration. The amendments to the claims do not materially affect the enablement rejection.

#### **Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is an incomplete method claim. The preamble states that it is a method for reducing pancreatic edema, however, there is no indication that the active agent is administered in an amount effective to achieve such, nor that such has been achieved.

The preamble of claim 26 indicates it to be a method of reducing pancreatic edema. However the body of the claim states that the active agent is administered "in an amount effective to prevent or treat edema". One cannot reduce edema that has not occurred. Further, the recitation of "an amount effective to....*treat*" edema does not correlate with the preamble statement that requires "reducing edema".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16-23, 25, 26, 40 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is the use of IL-6 inhibitors to treat acute pancreatitis. The exhaustive prosecution has established that both IL-6 and TNF are associated with acute pancreatitis, that IL-6 inhibits TNF-alpha, and TNF-alpha induces IL-6.

The prior art does not recognize IL-6 inhibitors as a treatment for acute pancreatitis, and presents information that does not give a clear picture of whether such treatment would be successful. As stated in the previous rejection under §103, Gross et al. teach that IL-6 concentrations are associated with acute pancreatitis; see page 525. Farkas et al. teach that experimental acute pancreatitis results in increased blood-brain barrier permeability (title), and that such is associated with increased IL-6 levels (page 149, paragraph bridging columns). However, the prosecution has evolved to center on the issue of predictability of inhibition of IL-6 in treating acute pancreatitis, and it has been determined that there is no reasonable expectation of success in doing so, as there is no preponderance of art that would support such.

With further respect to claims 25 and 26, the claims are drawn to reduction of pancreatic edema due to any cause, and not merely acute pancreatitis, and encompasses any and all pancreatitis. As there has been no predictability established for the model system used by

applicants being predictive of treatment of acute pancreatitis, it is only reasonable that the model system used cannot be predictive of other forms of pancreatitis.

At page 5 of the response filed 1/6/11, applicants argue that the Examiner failed to consider Exhibits G-K submitted with the previous response. The Examiner regrets the oversight. Applicants are reminded that the issue at hand is not whether administration of cerulean is used as a model system of acute pancreatitis, but rather that (a) administration of an IL-6 antibody at the same time as administration of cerulein, or prior to such administration, is not a model for treatment of acute pancreatitis, but rather a model of prevention of such, and (b) since there is no way to predict who will develop acute pancreatitis unless such is experimentally induced, the experiments in the specification are not enabling of prevention, except in an animal model system.

Exhibit G merely gives a list of references, and does not serve to show any information as to the issue at hand, which is whether of not pretreatment with an IL-6 inhibitor would treat existing acute pancreatitis.

Exhibit H did not use cerulean to induce acute pancreatitis, but rather used a choline-deficient ethionine supplemented diet, which to the Examiner's knowledge, is not cerulein. Further, the treatment started on day 1 of induction of pancreatitis. There was no measure of treating rodents already affected with acute pancreatitis. Finally, the active agent was not an IL-6 inhibitor, but rather risperidone, a serotonin inhibitor. Therefore, the reference is not germane to the issue at hand. There is "speculation", clearly identified as such, that acinar cell injury triggers local inflammatory reactions, and, "if (emphasis added) coincided with enhanced IL-6 release, leads to a systemic inflammatory response syndrome, which is responsible for the mortality." (see for example, the abstract). However, this is clearly labeled as conjecture, and as such is an invitation to experiment, and not probative of an expectation of success or lack thereof.

Exhibit I administered cannabinoids to rodents 30 minutes before administering cerulein, and 4 hours after. Thus, once again, the treatment began before the disease. It is further noted that cannabinoids have no bearing on the predictability of treating acute pancreatitis with IL-6 inhibitors. The last sentence of the publication indicates that the results "lay a basis for testing

the therapeutic value of cannabinoids as supplements to conventional analgesic therapy" for acute pancreatitis, indicating an invitation to experiment, which is not tantamount to a reasonable expectation of success.

Exhibit J states that cerulein was used as "baseline hydration" (page 671, 2nd column), and that severe acute pancreatitis was induced with glycodeoxycholic acid glycylglycine-sodium hydroxide buffered solution. Treatment with recombinant human activated protein C was measured .5-24 hours after induction.

Exhibit K is a publication about the use of cerulean as a model of acute pancreatitis, and does not address treatment of such. However, this issue is not in contention.

The issue at hand is a) whether treatment before the condition develops is predictive of treatment after acute pancreatitis occurs, and b) whether treatment by inhibition of IL-6 would be expected to be effective after acute pancreatitis has developed. None of the exhibits to which applicants refer show either treatment after development of acute pancreatitis, nor treatment of acute pancreatitis with any IL-6 inhibitor. Thus it remains that the sole working examples in the specification, which inhibit IL-6 prior to the induction of acute pancreatitis, are not enabling of the claims, which are drawn to the treatment of (existing) acute pancreatitis. Likewise, with regard to newly introduced claim 40, "ameliorating the severity of acute pancreatitis" is taken by the Examiner to mean that the condition is pre-existent. With regard to claim 41, the standing rejection applies as to the scope of the claim; the specification enables the method only in the model system, as there is no means of predicting whether and/or when a subject, for example a human, might develop acute pancreatitis. Since the invention is only enabled for prevention of such, and only in rodents, it is not enabling for the scope of the claims. There are no teachings as to how to predict when a subject will develop acute pancreatitis other than in model systems in which an agent is administered to cause such. It is not recognized in the art that one can predict the onset of acute pancreatitis, nor does the specification provide guidance as to such, other than it can be predicted in model systems in which a specific agent is administered to cause the acute pancreatitis.

At page 6, applicants argue that enablement of disease prevention should be considered to be enabling of disease treatment. This argument has been fully considered but is not deemed

persuasive because while it is true that an IL-6 inhibitor would block IL-6 activity at any time, it has not been established that prevention of IL-6 activity would have the same effect as attempting to stop IL-6 activity after the disease has developed. It is well known in the art that cytokines are not generally secreted at steady state levels in the course of a disease. In particular, see Ulich et al., discussed in the previous Office Action. Ulich, as characterized by applicants, teaches that If IL-6 is acting as an anti-inflammatory cytokine as part of an endogenous negative feedback loop, the person of ordinary skill in the art would expect that IL-6 would occur later in inflammation, rather than earlier. Thus, Ulich is evidence that cytokines are not expected to occur at static levels.

Accordingly, it remains that there is no consensus in the art.

In this particular case, given the teachings in the art, there is no predictability about whether administration of IL-6 would be beneficial to patients having acute pancreatitis, nor how and when such should be administered; clearly, looking at the most recent reference cited by applicants in their most recent submission, timing would be critical.

There are no working examples in which any anti-IL-6 molecule was administered to any animal or human either having acute pancreatitis, or an accepted model of such.

The claims do not specify how or when the active agent is to be administered.

Accordingly, the Examiner concludes that it is not predictable that the claimed invention would work at all, other than for the prevention of experimentally induced acute pancreatitis in rodents. Nor is there sufficient disclosure to allow the skilled artisan to practice the claimed invention without substantial experimentation. All applicants have presented is the germ of an invention, and an invitation to determine how to practice that invention. There is no consensus in the art of what the role of IL-6 in acute pancreatitis is, nor at what time during the course of the disease. As previously discussed, IL-6 might have positive or negative effects, depending upon what else is going on.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc. v. Novo Nordisk*, 42 USPQ 2d 100, (CAFC 1997), the court held that: “[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable” and that “[t]ossing out the mere germ of an idea does

not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot, following the guidance presented therein, practice the suggested method without first making a substantial inventive contribution.

Finally, at pages 6-7, applicants argue that claims 25, 26, 40 and 41 recite methods of "reducing pancreatic edema, "ameliorating the severity of acute pancreatitis, and "preventing the onset of acute pancreatitis", and thus encompass a scope that "is closer to, if not within, the prophylactic efficacy to which the office seeks to limit the evidence." With respect to claims 26 and 26, the Examiner maintains that there is evidence only for prevention of acute pancreatitis or its symptoms, and not for treatment after such has or have occurred. Further, the prevention is only enabled for model systems, as they are the only conditions under which onset can be predicted and thus prevented. With respect to claims 40 and 41, the enablement is discussed above, and found to be present only for model systems, as they are the only conditions under which onset of acute pancreatitis can be predicted. With specific respect to claim 41, drawn to "ameliorating" the severity of acute pancreatitis, the word "ameliorate" means to make better or improve something. Thus, it reads on both prevention and treatment, each of which have been amply dealt with above.

No claim is allowed.

#### **Conclusion**

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday from 8:00 A.M. to 4:30 P.M. Eastern Time, and Tuesday through Friday, 8:00 A.M. to 2:00 P.M. Eastern Time at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Jeffrey Stucker, at telephone number 571-272-0911.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to **571-273-0893**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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